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Long-term close follow-up of chorioretinal lesions in presumed ocular tuberculosis

THESE

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*Long-term close follow-up of chorioretinal lesions in
presumed ocular tuberculosis*

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*pour Le Doyen
de la Faculté de Biologie et de Médecine*



*Madame le Professeur Stephanie Clarke
Directrice de l'Ecole doctorale*

Summary:

Purpose:

To evaluate the long-term outcome (up to 7 years) of presumed ocular tuberculosis (TB) when the therapeutic decision was based on WHO guidelines.

Methods:

Twelve out of 654 new uveitic patients (1998-2004) presented with choroiditis and positive tuberculosis skin test (TST) (skin lesion diameter >15 mm). Therapy was administered according to WHO recommendations after ophthalmic and systemic investigation. The area size of ocular lesions at presentation and after therapy, measured on fluorescein and indocyanine green angiographies, was considered the primary outcome. Relapse of choroiditis was considered a secondary outcome. The T-SPOT TB test was performed when it became available.

Results:

Visual acuity (VA) significantly improved after therapy ($p=0.0357$). The mean total surface of fluorescein lesions at entry was 44.8 ± 20.9 (arbitrary units) and decreased to 32.5 ± 16.9 after therapy ($p=0.0165$). The mean total surface of indocyanine green lesions at entry was 24.5 ± 13.3 and decreased to 10.8 ± 5.4 after therapy ($p=0.0631$). The T-SPOT TB revealed 2 false TST-positive results. The mean follow-up was 4.5 ± 1.5 years. Two relapses out of 10 confirmed ocular TB was observed after complete lesion healing, 2.5 years and 4.5 years after therapy, respectively.

Conclusions:

A decrease of ocular lesion mean size and a mean improvement of VA were observed after antituberculous therapy. Our long-term follow-up of chorioretinal lesions demonstrated relapse of ocular tuberculosis in 10% of patients with confirmed ocular TB, despite complete initial retinal scarring.

ORIGINAL ARTICLE

Long-term close follow-up of chorioretinal lesions in presumed ocular tuberculosis

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CONCLUSIONS. A decrease of ocular lesion mean size and a mean improvement of VA were observed after antituberculous therapy. Our long-term follow-up of chorioretinal lesions demonstrated relapse of ocular tuberculosis in 10% of patients with confirmed ocular TB, despite complete initial retinal scarring.

KEY WORDS. Ethambutol, Isoniazid, Ocular tuberculosis, Pyrazinamide, Rifampicin, T-SPOT TB

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INTRODUCTION

The pathogenesis of tuberculosis (TB) is characterized by a primary infection, followed by a latent stage, then possible reactivation of the disease (1). The infection occurs after inhalation of small droplets containing a few *Mycobacterium tuberculosis* bacteria. The primary lesion produces a pulmonary scar, visible on chest X-ray, and the patient has a positive tuberculosis skin test (TST). Then, the disease enters a latent stage. Activation of the disease is only seen in 10% of individuals. About 5% of patients will develop active lesions within 2 years, and 5% later (1).

Ocular TB has a protean expression ranging from anterior uveitis to posterior uveitis or panuveitis. Focal, multifocal, and sometimes serpiginous-like choroiditis are a common manifestation of ocular TB and are associated with various degrees of ocular inflammation (vasculitis, cystoid macular edema, or vitritis) (2, 3). Other manifestations may be observed such as a solitary nodule, multiple nodules (nodules de Bouchut), or optic disc nodules (4-6).

Ocular TB is most often detected in the absence of active pulmonary lesions (7). The response of ocular disease to antituberculous agents (isoniazid or INH therapeutic test) has been suggested for the diagnosis of presumed intraocular

TB, but the increasing prevalence of drug-resistant strains has diminished its usefulness (8). The absence of any pulmonary lesion on chest X-ray and a negative TST do not exclude the disease (9, 10). Antituberculous therapy is thus often administered empirically, albeit toxic, prolonged, and costly. Moreover, false-positive TST tests can be seen because of cross-reactivity between *M tuberculosis* or *M bovis* antigens and previous bacillus Calmette-Guerin (BCG) vaccination (11, 12).

The World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) have published guidelines for the therapy of pulmonary and extrapulmonary TB (13). Therapeutic guidelines for latent TB, formerly known as "prophylaxis," consist of 300 mg/day INH for 9 months (previously 6 months). When active pulmonary lesions are present, the treatment is based on culture of bacteria and detection of resistance. In pulmonary TB, 4 antituberculous agents are required during the first 2 months followed by a bitherapy for 4 additional months. Treatment of ocular TB, however, remains controversial. Some authors propose the administration of quadritherapy (6, 14, 15) due to the poor intraocular bioavailability of antituberculosis agents, sometimes associated with steroids (14). According to the WHO recommendations, the choice of therapy depends largely on the presence of pulmonary lesions (5). Quadritherapy is mandatory in case of potential risk of resistance, present when the total number of bacteria is over 10^6 (13). There are hardly any reports in the ophthalmic literature on long-term follow-up and risk of disease relapse after therapy.

The aim of this longitudinal cohort study was to determine the long-term retinal pattern of consecutive cases of ocular TB in patients treated according to WHO and CDC guidelines. Clinical evaluation of the ocular lesions before and after antituberculous therapy, based on fundus photographs, fluorescein and indocyanine green (ICG) angiograms, was considered the primary outcome. Time to relapse was used as the secondary outcome during long-term follow-up of patients. Maximum follow-up was 7 years.

MATERIALS AND METHODS

All patients were seen at the uveitis clinic (Jules Gonin Eye Hospital) between October 1998 and October 2004 and the department of infectious diseases (Centre Hospitalier Universitaire Vaudois or CHUV). Both centers have a general authorization to perform retrospective analysis of their

patients. The study followed the tenets of the Declaration of Helsinki.

Included in the study were patients over 18 years old, fulfilling the criteria of presumed ocular TB, with a positive TST (described below) and active uveitis. Other tests to diagnose TB were not available at the start of the study. The TST was performed for all patients presenting with a granulomatous uveitis, vitritis, focal or multifocal choroiditis. Other specific causes of granulomatous uveitis were ruled out by ocular examination (uveitis specialist, Y.G.C.) and by systemic investigation with laboratory and radiologic workup (infectious disease specialists, M.K. and M.C.) (13).

Ocular examination comprised ocular history, visual acuity (VA), and slit-lamp biomicroscopy (topical administration of 10% phenylephrine and 0.5% tropicamide). Photographs were performed at the first visit and after treatment with antituberculous agents (16). Clinical evaluation of both eyes was repeated every month during therapy and then yearly until November 2007. Once available, the T-SPOT TB assay (described below) was performed in all patients between March and August 2005 (except one, lost to follow-up).

Clinical evaluation and the following laboratory workup were performed by M.K. and M.C.: full blood count, sedimentation rate; C-reactive protein, serum angiotensin-converting enzyme, lysozyme, serologic tests (Lyme disease, syphilis, toxoplasmosis, and cat-scratch disease), urine sedimentation rate and chest X-ray. Computerized tomography of the chest was performed when necessary.

Antituberculous agents were allocated according to the WHO and CDC recommendations (13), unless refused by the patient: no therapy when the systemic evaluation could not confirm the presence of systemic TB; 6 months therapy with 300 mg/day of INH (5 mg/kg; maximum 300 mg) alone in the presence of presumed systemic TB or latent TB (a primary infection was detected, but no active systemic disease); tritherapy or quadritherapy in the presence of systemic evidence of TB. Tritherapy consists of 300 mg/day of INH (5 mg/kg; maximum 300 mg), 600 mg/day of rifampicin (RFP) (10 mg/kg; maximum 600 mg), and 1500 mg/day of pyrazinamide (PZA) (25 mg/kg) for 2 months, followed by 4 months of INH and RFP. Quadritherapy consists of 300 mg/day of INH, 600 mg/day of RFP, 1500 mg/day of PZA, and 800 mg/day ethambutol (EB) for 2 months, followed by INH and RFP for 4 additional months. Systemic steroid therapy was given according to inflammatory disease activity.

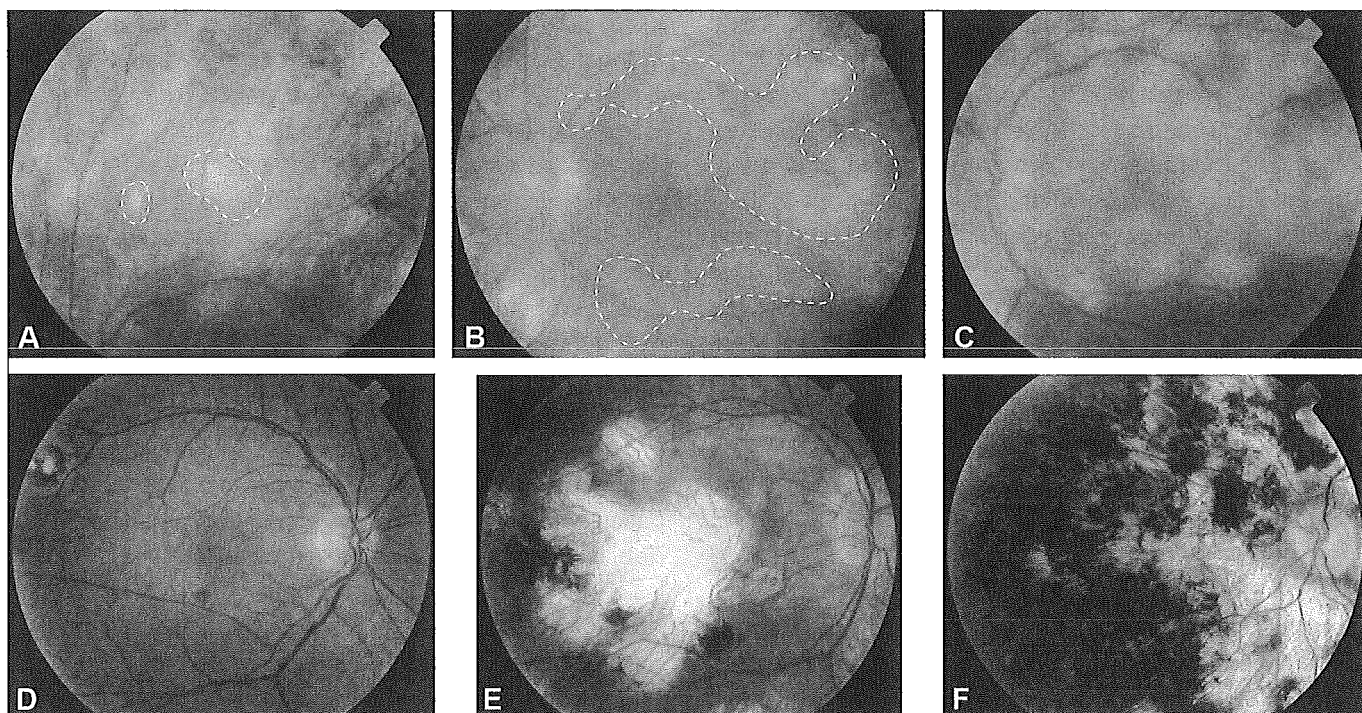


Fig. 1 - Standard fundus photographs. Grading of leakage. Grade 1 (A): 2 zones of slight leakage are surrounded by dashed lines; the retina appears swollen. Grade 2 (B): 2 large zones of leakage are visible along the arcades. Grade 3 (C): the posterior pole appears severely swollen. Grading of the pigmentation: slight (D), moderate (E), severe (F).

Fundus photographs and fluorescein and ICG angiograms

Bilateral color photographs with 9 primary eye positions (one of the posterior pole and 8 peripheral frames), panoramic fluorescein and ICG protocol were performed both at study entry and after therapy.

Uveitis activity was graded by an independent observer (M.D.) on masked fundus photographs and late frames of fluorescein angiograms (10–12 minutes after dye injection). Disease activity was scored according to retinal dye leakage and later scarring appearing as pigmentation of scars.

Both criteria of disease activity, leakage and pigmentation, were scored from 0 to 3: 0 = none, 1 = mild, 2 = moderate, 3 = severe (Fig. 1). Cystoid macular edema (CME) was evaluated on late frames of fluorescein angiograms, taken between 10 and 12 minutes after dye injection (0 = none, 1 = mild, 2 = moderate, 3 = severe) according to Miyake classification (17).

The size of the lesions (arbitrary units) was measured by the NIH image® software 1.58 on fluorescein and late phase (over 30 minutes) ICG angiograms. Angiograms were scanned

using a UMAX Astra 2200 Twain compatible scanner. After importing images into a Macintosh computer, the borders of ocular lesions were outlined and the area calculated.

The disease was bilateral in 4 patients. To avoid statistical biases, only one eye—the eye with maximal inflammation—was evaluated in this study.

Tuberculosis skin test

The test was performed with subcutaneous injection of 2 IU of RT23 antigen; this test was the gold standard test used in Switzerland for TB screening and is equivalent to 5 IU of standard antigens. Patients with an induration >15 mm were investigated in the infectious diseases department.

Gamma-interferon test: T-SPOT TB

Elispot detects cells producing interferon- γ (IFN- γ) after stimulation by *M tuberculosis* antigens (T-SPOT TB, Oxford Immunotec Ltd, UK). This Food and Drug Administration-registered test became available in Switzerland in March 2005. Peripheral blood mononuclear cells (PBMCs) of pa-

tients were added to microtiter wells coated with antibody to IFN- γ . Two *M tuberculosis*-specific antigens, which have no cross-reactivity with BCG vaccination (18, 19), and controls were added to stimulate any specific T cell. Secreted IFN- γ was captured by the coating antibody. After washing, a second antibody, conjugated to alkaline phosphatase and directed to a different epitope on IFN- γ , was added and bound to IFN- γ captured on the well surface. After washing, a substrate was added and formed an insoluble precipitate at the reaction site. The number of spots measured the frequency of *M tuberculosis*-sensitive cells. This test was performed to exclude the presence of false-positive TST in a population where the BCG vaccination was highly recommended from 1960 to 1970.

Statistics

Statistical significances were calculated using the Student *t* test. Values were expressed \pm SEM. The program JMP® 8, SAS Institute, Inc. (Cary, NC), was used for statistics.

RESULTS

Baseline information and treatments

Of the 654 new patients presenting at the Jules Gonin Eye Hospital with active uveitis, 12 (1.8%) fulfilled the criteria for focal, multifocal, or serpiginous-like choroiditis in presumed ocular TB (Tab. I). The median age was 38 years (range 23-73). The male to female ratio was 6:6. Four pa-

tients were born in Switzerland, 3 in Balkan countries, 3 in European countries, and 2 in Asia. In TST, the skin lesion was >15 mm and the median diameter 32.5 mm. The mean follow-up was 4.5 \pm 1.5 years (range 2-7 years). One patient (no. 8) left Switzerland 4 years after therapy but follow-up continued in Parma (Italy) with no relapse. The T-SPOT TB, which became available after antituberculosis therapy, allowed us to reinforce the diagnosis of presumed ocular TB. The T-SPOT TB was positive in 9 out of 11 patients (80%) and detected 2 false-positive TST. Choroidal lesions were present in all 12 patients. The disease was bilateral in 4 patients and choroiditis was present in 16 eyes. Ten patients presented with multifocal choroiditis and 2 with serpiginous-like choroiditis. In addition, 2 patients presented with associated vitritis and 6 with CME (Tab. II). Seven patients had a normal chest X-ray, 2 had TB lesions, 2 had a calcified granuloma, and 1 had left parahilar lymphadenopathy with a small nodule in the lingula on computerized tomography. Two patients received no antituberculous therapy (Tab. I). The first one (patient 9) did not fulfill the WHO or CDC criteria; the treatment was not required due to good VA and small lesions. The second one (patient 5) fulfilled diagnosis criteria for tuberculosis but refused INH therapy and the ocular lesion became inactive within 2 months in the absence of treatment. Among the 10 treated patients (Tab. I), 6 received monotherapy, 1 tritherapy, and 3 quadritherapy. None of the patients had to stop antituberculous therapy because of side effects. In addition to antituberculous therapy, all except 2 patients underwent a course of oral prednisone, starting at a dose of 40 to 60

TABLE I - CLINICAL CHARACTERISTICS AND TREATMENT OF PATIENTS WITH PRESUMED INTRAOCULAR TUBERCULOSIS

Patient	Age, y	Sex	Eye	Posterior findings	TST, mm	T-spot TB ^a	Chest radiograph	Antituberculosis therapy (mo)	Steroid therapy, mo ^b	Relapse ^c	Follow-up, y
1	66	F	Both	Multifocal choroiditis	50	Positive	Normal	INH (6)	7		4
2	33	M	Both	Multifocal choroiditis	23	Positive	Lymphadenopathy	INH, RFP (6), PZA (2)	2		7
3	34	F	Right	Vitritis, multifocal choroiditis	50	Positive	Normal	INH, RFP (6), EB, PZA (2)	9		7
4	58	M	Right	Multifocal choroiditis	50	Positive	Normal	INH (6)	6		3
5	42	M	Left	Multifocal choroiditis	18	Positive	Calcified granuloma	None	2	Yes	5
6	28	M	Both	Serpiginous-like choroiditis	20	Positive	Normal	INH (6)	1	Yes	3
7	66	M	Left	Vitritis, multifocal choroiditis	22	Positive	Calcified granuloma	INH (6)	2		2
8	66	F	Right	Multifocal choroiditis, large area	22	Not done	Normal	INH, RFP (6), EB, PZA (2)	8		3
9	32	M	Right	Multifocal choroiditis	17	Negative	Normal	None	None		3
10	73	F	Both	Multifocal choroiditis	50	Positive	Tuberculosis lesions	INH (6)	None		4
11	24	F	Right	Multifocal choroiditis	18	Negative	Normal	INH (6)	2		7
12	23	F	Left	Serpiginous-like choroiditis	50	Positive	Tuberculosis lesions	INH, RFP (6), EB, PZA (2)	2		4

EB = ethambutol; INH = isoniazid; PZA = pyrazinamide; RFP = rifampicin; TB = tuberculosis; TST = tuberculosis skin test.
^a T-spot TB test was performed after antituberculosis therapy, when the test became available.
^b Steroid therapy was tapered over the number of months shown in the column.
^c Relapse at 4.5 years in the contralateral eye (patient 5) and at 2.5 years (patient 6).

mg/day and gradually tapered off.

Table II shows the evolution of VA and ophthalmoscopic retinal images. In the case of bilateral disease, the eye with maximal inflammation was reported. Mean VA at the time of presentation was 0.22 ± 0.06 logMAR, and improved to 0.11 ± 0.05 logMAR after therapy ($p=0.0357$). Eleven patients showed improvement in ocular inflammation by reduction of fluorescein lesions after therapy. The mean total surface of fluorescein lesions was 44.8 ± 20.9 (arbitrary units, range 0.7-245.1) at entry and significantly decreased to 32.5 ± 16.9 (range 0.3-192.5) after therapy ($p=0.0165$). The mean total surface of ICG lesions was 24.5 ± 13.3 (range 0-166.1) and 10.8 ± 5.4 (range 0-66.7) at entry and after therapy, respectively ($p=0.0631$). At entry, leakage was scored 1 or 2 in all patients and CME between 0 and 2. Therapy induced significant reduction of both leakage ($p<0.001$) and CME ($p=0.0135$). Pigmentation had a tendency to increase after therapy ($p=0.0955$), corresponding to tissue scarring after the resolution of active inflammation.

During follow-up, 2 out of 10 patients (patients 5 and 6) (10%) confirmed with ocular TB presented a relapse of ocular lesions despite complete scarring (Tabs. I and II). Both patients were later revealed positive for T-SPOT TB.

On presentation, patient 5 had a small paramacular active

lesion associated with peripheral inactive multifocal choroiditis. He was positive for toxoplasmosis and received a 2-month antitoxoplasmosis therapy with corticosteroids. A small pulmonary nodule was discovered on chest X-ray and, because of a positive TST, an additional 6-month course of INH therapy was proposed. The patient refused further therapy after the resolution of ocular symptoms. A relapse of the disease was observed 4.5 years later in the contralateral eye with multifocal choroiditis lesions. The history of patient 6 is detailed below.

Case report: patient 6

A 28-year-old man of Balkan origin presented with blurred vision in the left eye of 7 days duration. He had immigrated from Kosovo 12 years previously and had never received BCG vaccination. His brother had been treated for presumed ocular TB. Past medical and surgical histories were otherwise unremarkable. Chest X-ray was normal (Tab. I). Visual acuity was +1.0 logMAR in the left eye and 0 logMAR in the right eye (Tab. II). There was no anterior segment or vitreous inflammation. Funduscopy examination showed bilateral areas of choroiditis around the optic nerve (Fig. 2, A and C). Both TST (20 mm) and T-SPOT TB were positive.

TABLE II - VISUAL ACUITY AND CHARACTERISTICS OF PRESUMED TUBERCULOSIS LESIONS BEFORE AND AFTER THERAPY

Patient no.	Eye	Initial VA logMAR	Final VA logMAR	Initial fluorescein surface ^a	Final fluorescein surface ^a	Initial ICG surface ^b	Final ICG surface ^b	Initial leakage	Final leakage	Initial pigmentation	Final pigmentation	Initial CME	Final CME
1	R	+0.4	+0.5	50.05	8.06	5.92	4.09	2	1	0	2	1	0
2	L	0	0	10.14	0.29	28.26	0.03	1	0	0	0	0	0
3	R	0	0	1.34	1.44	2.02	4.35	2	1	0	0	1	0
4	R	+0.5	+0.2	10.51	5.86	0.00	0.00	1	1	0	0	1	1
5	L	+0.4	0	22.49	22.13	10.83	7.26	1	0	2	2	1	0
6	R	0	0	18.61	16.12	17.92	17.13	1	0	1	1	0	0
7	L	+0.5	+0.1	8.50	4.20	2.20	2.10	1	0	1	1	2	0
8	R	+0.5	+0.2	245.12	192.47	28.92	6.50	2	0	1	2	2	0
9	R	0	0	2.45	1.75	1.84	2.01	1	0	1	1	0	0
10	R	+0.2	+0.3	40.66	30.31	28.55	18.85	1	0	1	1	0	0
11	R	0	0	0.66	0.58	1.54	0.74	1	0	1	1	0	0
12	L	+0.1	0	127.37	106.37	166.08	66.68	2	1	1	1	0	0

CME = cystoid macular edema; ICG = indocyanine green; VA = visual acuity.

^a Measurement of lesions on fluorescein angiography.

^b Measurement of lesions on indocyanine green angiography.

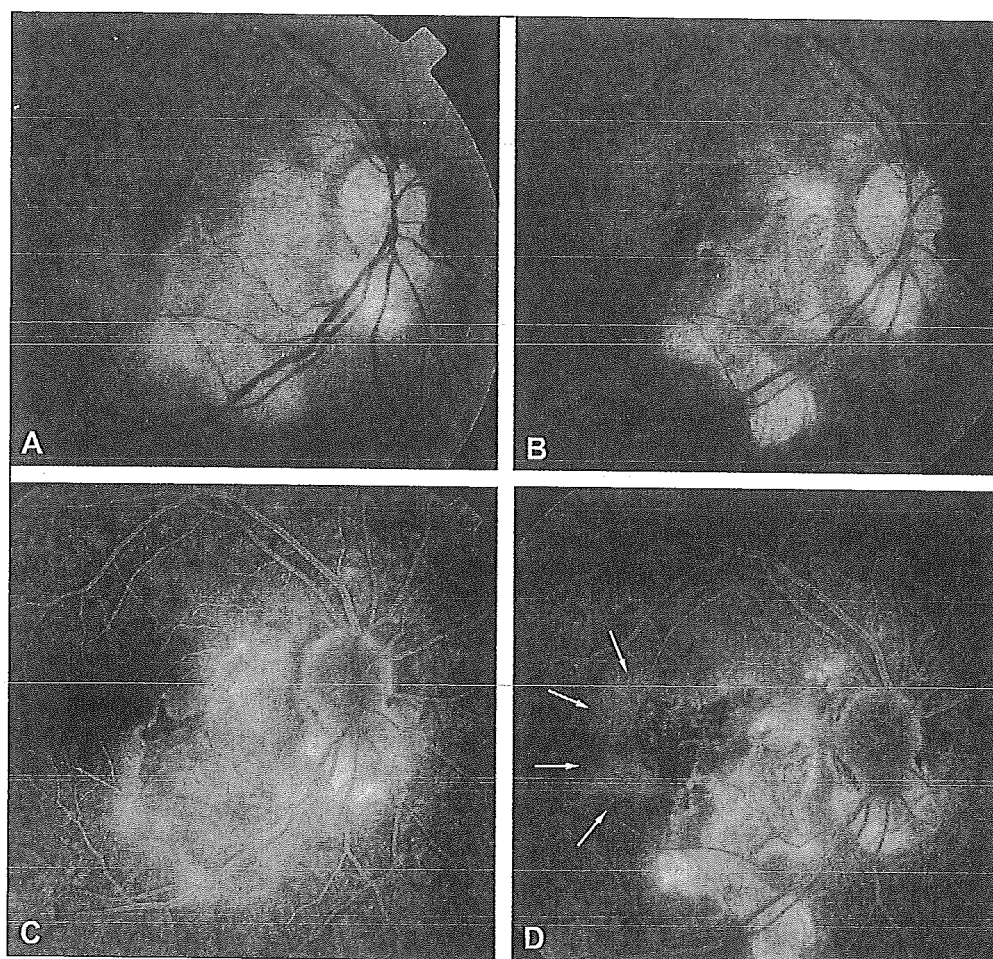


Fig. 2 - Initial fundus photograph (A) and fluorescein angiography (C) during the first episode of ocular inflammation. A relapse of inflammation is seen 2.5 years after INH therapy (fundus photograph [B], fluorescein angiography [D]). Fluorescein leakage is visible (arrows) during the late stage of angiography around the new lesion.

The patient was treated with a 6-month course of INH and oral corticosteroids. The ocular findings improved over the following weeks and the steroids tapered, then withdrawn after 1 month. Visual acuity was +0.4 logMAR in the left eye and the lesions appeared inactive.

At 2.5 years after INH treatment, the patient presented with decreased vision in the right eye, with a VA of +0.5 logMAR. Left eye VA was +0.5 logMAR. There was no anterior uveitis or vitreous inflammation. Posterior segment examination showed enlargement of the cicatricial area accompanied by yellowish-white edges characteristic of disease flare-up on the right eye (Fig. 2, B and D). In the left eye, posterior segment examination showed new multiple chorioretinal lesions. Due to the relapse of choroiditis, the patient was undergoing antituberculous quadritherapy associated with oral corticosteroids. One month after presentation, VA improved to +0.1 logMAR in the right eye, and +0.2 logMAR in the left eye. The lesions resolved and appeared cicatricial.

DISCUSSION

The presence of a focal, multifocal, or serpiginous-like (2, 3, 20, 21) choroidal lesion, associated with a positive TST, is highly suggestive of ocular TB. Without a direct bacterial isolation in ocular fluid, the treatment remains challenging. Up to 60% of patients with presumed ocular TB have no evidence of pulmonary TB (7, 9, 10). Negative chest radiograph and negative sputum culture results do not exclude the diagnosis.

In this study, 6 patients were initially treated with antituberculous monotherapy, 1 with tritherapy, 3 with quadritherapy. Two patients received no antituberculosis treatment.

Therapeutic guidelines of the WHO and CDC were mostly based on potential risk of resistance development and further transmission of the disease through active pulmonary TB (13). At the time of the study, ophthalmic literature proposed for ocular TB treatment either INH alone (5) or combined therapies (2, 7). The question of

monotherapy versus tritherapy or quadritherapy remains open. In the presence of a small ocular lesion, the systematic introduction of quadritherapy may expose the patient to severe side effects such as liver insufficiency and hepatic necrosis.

Presumed ocular TB should be treated by both anti-infectious and anti-inflammatory drugs (6). Antituberculosis therapy combined with systemic corticosteroids was shown to be efficient in treating presumed TB uveitis (5, 7). A retrospective analysis demonstrated the benefit of quadritherapy combined with steroids over steroids alone (14).

Mean VA significantly improved after therapy. However, VA could not be considered a major outcome since the location of the ocular lesion could interfere with VA.

The first outcome chosen to evaluate the disease progression was the size of retinal lesions as measured on late-phase ICG and fluorescein angiograms before and after therapy. Indocyanine green angiography is a useful method to determine the extent of the choroidal lesion and to evaluate treatment results in TB patients. We demonstrated that the mean total surface of ICG lesions significantly decreased after therapy. The size of ocular lesions diminished in 10 patients. One patient (no. 9) showed lesion size increase: he did not receive antituberculous treatment initially.

After therapy, a significant decrease in the mean total surface of lesions was observed in our fluorescein angiograms.

Because of our extended follow-up over a long period of time (mean of 4.5 years), we demonstrated that ocular TB could be reactivated; 2 cases that had shown a complete scarring of initial retinal lesions presented a relapse of ocular disease. Patient 5 was at risk of relapse as he refused treatment. Indeed, 4.5 years after the initial manifestations of presumed ocular lesions, he developed new lesions in the contralateral eye. Patient 6 had a relapse 2.5 years after treatment with INH, suggesting an INH-resistant strain. The relapse of ocular TB, despite scarring of initial ocular lesions, is interestingly comparable to reactivation of pulmonary TB, as described by Small et al (1).

Patient 9, followed up without treatment, showed scarred and unchanged intraocular lesions, suggesting that the disease was not due to ocular TB. Indeed, if his TST was positive, T-SPOT TB appeared later negative. Patient 11 was treated with a 6-month course of INH but retrospec-

tively tested negative for T-SPOT TB. This patient was probably overtreated because of the confounding effect of BCG vaccination (22).

Introduction in 2005 of the new T-SPOT TB allowed us to confirm the diagnosis of presumed ocular TB in patients previously treated. The 2 false-positive TST patients were vaccinated as children. The reaction of TST on BCG-vaccinated, uninfected patients has been largely described and T-SPOT TB should be preferred for diagnosis in such populations (11, 12, 14, 20). This test avoids unnecessary chemoprophylaxis associated with toxic effects and high costs.

In conclusion, our study evaluates the outcome of patients presenting with multifocal choroiditis or serpiginous-like choroidopathy and a strong positive TST over 7 years. T-SPOT TB is a necessary diagnostic test to initiate treatment of presumed ocular TB. In our study, antituberculosis treatment significantly reduced lesions measured on ICG and fluorescein angiograms. The long-term monitoring of chorioretinal lesions showed that 10% of patients (2 out of 10 patients with confirmed TB) presented an ocular relapse despite complete initial ocular lesions scarring.

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